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Granulates for multiparticulate controlled-release oral compositions.

Granulates for multiparticulate controlled-release oral compositions comprising biologically active substances in solid dispersion with an acid-resistance and/or release-limiting compound, the solid dispersion being mixed with water-insoluble carrier particles, and the preparation of such granulates. Preferred biologically active substances are corticosteroids, non-steroidal anti-inflammatory drugs and bismuth compounds. The granules have a preferred particle size of less than 1 mm.

EP 0 375 063 A1

### Granulates for multiparticulate controlled-release oral compositions

This invention relates to granulates for multiparticulate controlled-release oral compositions comprising biologically active substances, targeted to predetermined parts of the intestine and especially to the lower part thereof, and to oral compositions, containing such granulates.

When the active principle of an oral composition (in a single-unit or multiparticulate product) is to be targeted to the intestine, it is conventionally coated by a single or multiple layer of an acid-resistant and/or slowly-releasing coating. Currently a considerable number of substances and mixtures are known for use in such coatings. European Patent Application 0040590 describes the coating of a core containing a therapeutically active substance by a single layer comprising an acid-resistant polymer and a water-insoluble polymer. A multiple-layered coating is described in U.S. Patent 3,431,338, where a drug-containing nucleus is coated successively with an acid soluble, alkali-resistant material, a water-soluble intermediate layer and an outer alkali-soluble, acid-resistant layer. In practice, the coated preparations are often unreliable and besides their production is cumbersome. Therefore, a need exists for improvement of intestinal drug targeting.

A further development is to use the concept of solid dispersion of the active principle in the release-modifying substance as an alternative to coating the active principle with the release-modifying substance. A solid dispersion, which is to be clearly distinguished from simple mechanical mixes, has been defined as a dispersion of one or more active ingredients in an inert excipient at solid state prepared by the melting (fusion), solvent, or melting-solvent method (J.L. Ford, *Pharm Acta Helv.* 67, 1988, 69). The concept of solid dispersion was introduced by K. Sekiguchi and N. Ohi (*Chem. Pharm. Bull.* 9, 1961, 868), to improve the bioavailability of a poorly water-soluble drug by dispersing it in a water-soluble excipient. The bulk of subsequent publications to date still concerns such enhanced-release products. But it has also been recognized that a similar concept can be applied to sustained-release products. One example is Japanese Patent Application (Kokai) 61,078,733, which discloses an amorphous solid preparation intended to dissolve in the intestine, comprising (a) a non-steroid type anti-inflammatory agent such as indomethacin and (b) one or more pH-dependent high molecular compounds, such as a copolymer of methacrylic acid and methyl methacrylate. It is manufactured by dissolving (a) and (b) in a common solvent, removing the solvent and pulverising the solid formed. Only grains falling within the required size are used, which of course involves loss of substance. Besides, when these grains are to be further processed into tablets, they have to be granulated first, a process in the course of which there exists a danger of adversely influencing the glass-like consistency of the solid dispersion, thus defeating its purpose of acid resistance.

The deposition of solid dispersions of the enhanced-release type on water-soluble carrier particles such as lactose, or on particles of calcium hydrogen phosphate which is soluble in gastric fluid has been proposed by K.H. Kim and C.J. Jarowski (*J. Pharm. Sci.* 68, 1977, 1536) and by J.L. Ford and M.H. Rubinstein (*Pharm. Acta Helv.* 55 1980 1), respectively.

The deposition of solid dispersions of the acid-resistant type on a water soluble inert core material (sucrose) has been described by A. Hasegawa et al. (*Chem. Pharm. Bull.* 33 1985 1615). This method involves a relatively cumbersome procedure of spray-coating the solid dispersion onto the water-soluble sucrose cores, for which a special apparatus is required. The thus coated sucrose particles are spherical and smooth, and they cannot be compressed into tablets without an extra step of granulation. Besides, this method is not suitable for solid dispersions of the release-limiting (pH-independent) type since these solid dispersions will allow already in the acid environment of the stomach the occurrence of aqueous diffusion, which will dissolve the cores, changing the form of the particles and making the release characteristics unpredictable and uncontrollable.

It has now been found that water-insoluble carrier particles do not have the above disadvantages, and that granulates for multiparticulate oral compositions wherein a biologically active compound is incorporated in solid dispersion with an acid-resistant or release-limiting compound can be prepared more efficiently and effectively by mixing this solid dispersion with water-insoluble carrier particles.

When water-insoluble carrier particles are used, they can simply be mixed with the dispersion before it is solidified, without any need to actively deposit the solid on the carrier cores. After the complete mixture has solidified, it is further processed to a granulate according to granulation methods known in the art, such as oscillating-sieving or extrusion.

The process according to the invention is very versatile since it is applicable to both acid-resistant and release-limiting preparations. The process is also very efficient since no special apparatus is required for the simple step of mixing the water-insoluble carrier particles with the dispersion, and since due to the granules being irregular in shape and porous they can be immediately compressed into tablets.

Thus, the present invention provides a method for preparing a granulate for a multiparticulate oral composition based on the concept of solid dispersion, whereby a biologically active substance is dispersed in an acid-resistant or release-limiting substance using the melting, the solvent or the melting-solvent method, characterized in that before the dispersion is solidified it is mixed with water-insoluble carrier particles whereafter the complete mixture is further processed according to granulation methods known in the art.

The invention also provides granulates for multiparticulate oral compositions comprising a biologically active substance in solid dispersion with an acid-resistant and/or a release-limiting compound, characterized in that the solid dispersion is mixed with water-insoluble carrier particles.

It will be appreciated that in principle any biologically active compound can be incorporated in the granulates for multiparticulate oral compositions of this invention, and in particular those compounds, e.g. the therapeutic (poly) peptides, which are sensitive to acid or to digestive enzymes and those which are disagreeable to the stomach, but that the main application of this invention lies with compounds which are meant to act locally in the intestine. Examples of the latter are corticosteroids and non-steroidal anti-inflammatory compounds, especially beclomethasone 17,21-dipropionate and 5- or 4-amino-salicylic acid or their derivatives. Further examples are bismuth compounds, especially Colloidal Bismuth Subcitrate. It will be appreciated that two or more biologically active compounds can also be incorporated in a composition according to the invention.

Acid-resistant and release-limiting compounds to be used in the compositions according to the invention may be any one or a combination of the compounds known for this purpose in the art. Examples of known acid-resistant compounds are polymethacrylates, especially those known under the name of EUDRAGIT-L and -S, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, and shellac. EUDRAGIT-S has been found to be a preferable acid resistant compound.

Examples of known release-limiting compounds are the polymethacrylates known under the name EUDRAGIT-RL, -RS and -NE, ethylcellulose and polyvinyl acetate, fatty acids such as stearic acid, fatty acid esters such as PRECIROL, long chain aliphatic alcohols such as cetyl, stearyl, cetostearyl and myristyl alcohol, hydrogenated vegetable oils such as hydrogenated castor oil and hydrogenated cottonseed oil, waxes such as bees wax and distilled monoglycerides such as glyceryl monostearate. EUDRAGIT-RS has been found to be a preferable release-limiting compound.

The percentage of the biologically active compound (w/w) in the solid dispersion can vary between 0.01-99%, depending on the the components used. When the biologically active compound is a corticosteroid such as beclomethasone 17,21-dipropionate its percentage (w/w) in the solid dispersion is preferably 0.1-40%, more preferably 5-15%. When the biologically active compound is a non-steroidal anti-inflammatory compound such as 5- or 4-amino-salicylic acid its percentage (w/w) in the solid dispersion is preferably 20-90%, more preferably 50-80%.

For the dispersion of the biologically active material in the acid-resistant or release-limiting substance, an organic or an aqueous solvent may be used.

As an organic solvent, methylene chloride has been found to be useful to disperse steroids, such as beclomethasone 17,21-dipropionate, in release-limiting substances. For the dispersion of said steroids in acid resistant substances, and of non-steroidal anti-inflammatory compounds, such as 5- or 4-amino-salicylic acid in both acid-resistant and release-limiting compounds, a mixture of about equal weights of ethanol and methylene chloride has been found to be very useful as the solvent.

When an aqueous solvent is employed to disperse a water-soluble biologically active substance, e.g. a therapeutic peptide, in the acid-resistant or release-limiting compound, aqueous polymeric dispersions have been found to be particularly useful as the aqueous solvent. Examples of these are aqueous dispersions of polymethacrylates such as EUDRAGIT-L-30-D, EUDRAGIT-RL-30-D, EUDRAGIT-RS-30-D and EUDRAGIT-NE-30, -40 or -50D, aqueous dispersions of submicron ethylcellulose spheres (AQUACOAT) and aqueous dispersions of submicron cellulose acetate phthalate spheres (AQUATERIC).

Examples of water-insoluble carriers to be used, singly or in combination, in the compositions according to the invention are powdered cellulose, microcrystalline cellulose, starches, colloidal silicon dioxide, bentonite, magnesium aluminum silicate and kaolin. Microcrystalline cellulose, such as is known under the proprietary name AVICEL, has been found to be a preferred carrier.

The preferred mean size of the carrier particles is about 0.1 mm, and the preferred mean particle size of the granulate (carrier plus solid dispersion) is 0.1-2 mm, more preferably 0.5-1.2 mm.

The granulates according to the invention can be incorporated in any of the preparations for oral application known in the art, such as sachets, capsules and, preferably, tablets, optionally also containing pharmaceutically acceptable excipients.

Tablets containing the granulates according to the invention have the practical advantages which are inherent to tablets in general, and additionally they have the advantage of being multi-particulate compositions, in that they disintegrate in the stomach, releasing the granules, which are small enough to leave the stomach rapidly and reliably. Alternatively, tablets containing the granulates according to the invention can be left to disintegrate in a small amount of water, rendering a homogeneous, drinkable dispersion.

It is known, e.g. from S.S. Davis et al., GUT 1986 27 883-892, that the gastric emptying of multiparticulate oral compositions resembles that of liquid dosage forms and differs from that of the bigger single units. While the intestinal transit time is approximately the same for the three dosage forms in both fasted and fed individuals, the gastric emptying of single units which do not disintegrate in the stomach tends to be slow and erratic, especially from a full stomach. Therefore there is an inherent advantage to multiparticulate dosage forms, above single-unit tablets.

The invention therefore also provides multiparticulate controlled-release oral compositions, in particular tablets, containing the granulates of the invention.

The following examples illustrate the invention.

#### Example 1

100 g of the acid-resistant EUDRAGIT-S were dissolved in a mixture of 240.5 g methylene chloride and 240.5 g ethanol 96%. Then, 15 g beclomethasone 17,21-dipropionate was dissolved in the above EUDRAGIT-S solution, and this solution was slowly (in 5 minutes) added to 385 g of the water-insoluble carrier AVICEL PH 102 in a planet mixer, working at 60 revolutions per minute. The complete mixture was partially dried during one hour at 50 °C, to a solvent content of 10-15%, and subsequently passed through an oscillating sieve of 1.0 mm apertures. The resulting granulate was further dried during 12 hours at 50-60 °C, to constant weight. The batch of granules, now ready for further processing, had a total weight of about 500 grams. 50 grams of it had a free volume of 170 ml. Its residual content of ethanol and methylene chloride, determined by GLC, was 1.5% and 0.015%, respectively.

The granules had the following particle size distribution:

Dimensions	Percentage of total
> 1000 µm	0.9
1000-800 µm	4.6
800-600 µm	19.4
600-400 µm	33.7
400-200 µm	29.4
< 200 µm	12.0

Thermal analysis proved the material of the solid dispersion to be different from a simple mechanical mix of the same concentrations of beclomethasone 17,21-dipropionate crystals and EUDRAGIT-S. While the mix demonstrated a sharp endotherm at 210 °C which is characteristic of beclomethasone 17,21-dipropionate, the solid dispersion had no endotherm up to 230 °C.

The content of beclomethasone 17,21-dipropionate in the granules was 3.0% w/w, as determined by HPLC.

#### Example 2

The disintegration adjuvants Kollidon-CL and Avicel PH 102, both in the quantities of 28 g, were added to 500 g of the granules of Example 1 and mixed during 10 minutes. Subsequently 5.5 g of the lubricant magnesium stearate was added and mixed during a further 2 minutes. The mass was then fed to an excenter press tableting machine, producing concave tablets having a diameter of 7 mm, a hardness of 8-11 Kp and a disintegrating time (into the granules), in 0.1 N HCl at 37 °, of 3-5 minutes. The tablets weighed 112.3 mg apiece, containing 3 mg beclomethasone 17,21-dipropionate and 20 mg EUDRAGIT-S.

The dissolution rate of these tablets was tested according to USP-XXI at 37°, with the paddle stirred at 75 rpm. One tablet was put in a medium of 400 ml 0.1 N HCl + 2% cetomacrogol 1000 (pH 1.3). After 30 minutes the pH was raised to 6.5 or 7.0 by adding 45 and 50 ml respectively of 20% Na<sub>3</sub>PO<sub>4</sub>·12H<sub>2</sub>O and making up to 500 ml with water, after which the pH was checked and exactly adjusted using a few drops of 4N NaOH or 6N HCl. Beclomethason 17,21-dipropionate was detected in samples of the medium taken at different time, whereby the HPLC method was used for quantification against a standard of 8 µg/ml beclomethason 17,21-dipropionate in phosphate buffer of pH 7.0 + 2% cetomacrogol 1000. The results, as shown in figure 1, clearly demonstrate a pH-dependant release.

### Example 3

62.5 g of the release-limiting compound EUDRAGIT-RL were dissolved in 300 g methylene chloride. Then 7.5 g beclomethason 17,21-dipropionate was dissolved in the above EUDRAGIT-RL solution, and this solution was slowly (in 5 minutes) added to 180 g of AVICEL PH 102 in a planet mixer, working at 60 revolutions per minute. The complete mixture was partially dried during one hour at 50°C. to a solvent content of 10-15%, and subsequently passed through an oscillating sieve of 1.0 mm apertures. The resulting granulate was further dried during 12 hours at 50-60°C. to constant weight of about 250 grams. 50 grams of it had a free volume of 198 ml. Its residual content of ethanol and methylene chloride, determined by GLC, was 0.012%.

The granules had the following particle size distribution:

Dimensions	Percentage of total
> 1000 µm	2.6
1000-800 µm	21.3
800-600 µm	30.2
600-400 µm	28.0
400-200 µm	14.9
< 200 µm	5.0

Thermal analysis proved the material of the solid dispersion to be different from a simple mechanical mix of the same concentrations of beclomethason 17,21-dipropionate crystals and EUDRAGIT-RS. While the mix demonstrated a sharp endotherm at 210°C which is characteristic of beclomethason 17,21-dipropionate, the solid dispersion had no endotherm up to 230°C.

The content of beclomethason, 17,21-dipropionate in the granules was 2.75% w/w, as determined by HPLC.

### Example 4

The disintegration adjuvants Kollidon-CI and AVICEL PH 102, both in the quantities of 12.5 g were added to 222.5 g of the granules of Example 3 and mixed during 10 minutes. Subsequently 2.5 g of the lubricant magnesium stearate was added and mixed during a further 2 minutes. The mass was then fed to an excenter press tableting machine, producing concave tablets having a diameter of 7 mm, a hardness of 6-7 kp and a disintegrating time (into the granules), in 0.1 N HCL at 37°C, of 3-5 minutes. The tablets weighed 117 mg apiece, containing 3 mg beclomethason 17,21-dipropionate and 28 mg EUDRAGIT-RL.

The dissolution rate of these tablets was tested in 300 ml pH 7 phosphate buffer + 1% cetomacrogol 1000 in a beaker of 400 ml. The magnetic stirrer had a rate of 600 rpm. Beclomethason 17,21-dipropionate was detected in samples of the medium taken at different time, whereby the HPLC method was used for quantification, against a standard of 8 µg/ml beclomethason 17,21-dipropionate in phosphate buffer of pH 7.0 + 1% cetomacrogol 1000. The results, as shown in figure 2, clearly demonstrate a sustained release.

Example 5

75 g of the release-limiting ethylcellulose and 75 g of hydrogenated castor oil were dissolved in 1175 g methylene chloride. Then 500 g 5-amino-salicylic acid was dispersed in the above solution, and this dispersion was added in 2 minutes to 450 g of the water-insoluble carrier powdered cellulose in a planet mixer, working at 60 revolutions per minute. The complete mixture was subsequently passed through a sieve of 1.0 mm apertures. The resulting granulate was dried during 12 hours at 50-60°C, to constant weight.

The dissolution rate of these granules was tested according to USP-XXI at 37°C, with the paddle stirring at 100 rpm. 555 mg granules were put in 1000 ml of phosphate buffer medium of pH 7.5 to which was added 0.1% PLURONIC F68. At time intervals upto 12 hours the absorbance at 326 nm was measured using a spectrophotometer equipped with a continuous-flow sampling system. The 5-amino-salicylic acid content was calculated using the absorbance value of a standard of 260 µg/ml of 5-amino-salicylic acid in phosphate buffer of pH 7.5, containing 0.1% PLURONIC F68.

The results, as shown in figure 3, clearly demonstrate a sustained release from the granules.

**Claims**

1. Method for preparing a granulate for multiparticulate controlled-release oral compositions based on the concept of solid dispersion, whereby a biologically active substance is dispersed in an acid-resistant or release-limiting substance using the melting, the solvent or the melting-solvent method, characterized in that before the dispersion is solidified it is mixed with water-insoluble carrier particles whereafter the mixture is further processed according to granulating methods known in the art.
2. A granulate for multiparticulate controlled oral compositions comprising a biologically active substance in solid dispersion with an acid-resistant and/or release-limiting compound, characterized in that the solid dispersion is mixed with water-insoluble carrier particles.
3. A granulate according to claim 2, characterized in that the biologically active substance is a corticosteroid.
4. A granulate according to claim 3, characterized in that the corticosteroid is beclomethasone 17,21-dipropionate.
5. A granulate according to claim 2, characterized in that the biologically active substance is a non-steroidal anti-inflammatory drug.
6. A granulate according to claim 5, characterized in that the anti-inflammatory drug is 5 or 4-amino-salicylic acid, or a derivative thereof.
7. A granulate according to claim 2, characterized in that the biologically active substance is a bismuth compound.
8. A granulate according to claim 7, characterized in that the bismuth compound is Colloidal Bismuth Subcitrate.
9. A granulate according to any of claims 2-8, characterized in that the acid-resistant compound is EUDRAGIT-S.
10. A granulate according to any of claims 2-8, characterized in that the release-limiting compound is EUDRAGIT-RS.
11. A granulate according to any of claims 2-10, characterized in that the water-insoluble carrier is microcrystalline cellulose.
12. A granulate according to any of claims 2-11, characterized in that the individual granules have a mean particle size of 0.1-2 mm.
13. A multiparticulate controlled-release oral composition, containing a granulate according to any of claims 2-12.
14. A multiparticulate controlled-release oral composition according to claim 13, characterized in that it is a tablet.

FIGURE 1

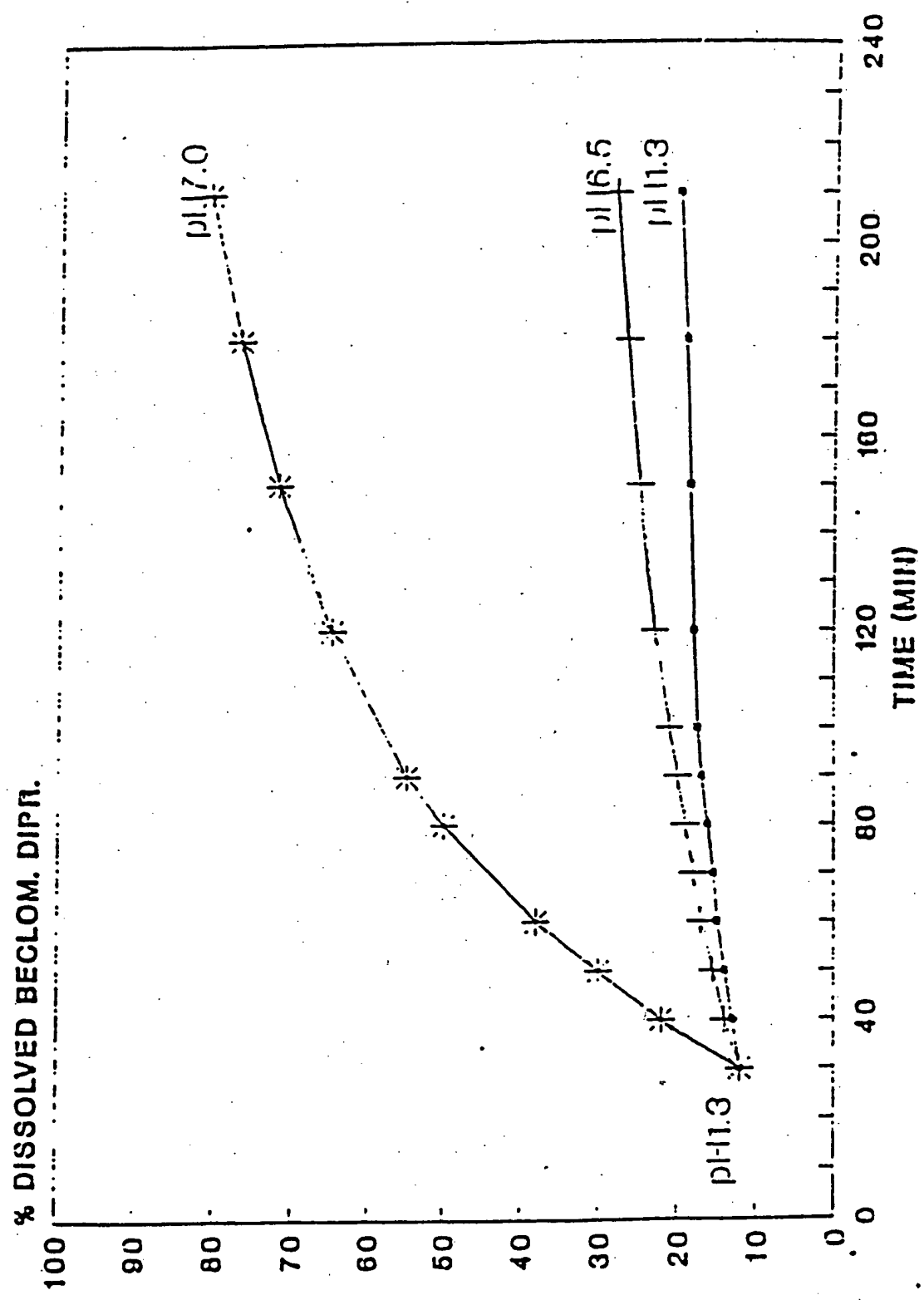


FIGURE 2

% DISSOLVED BECLOM. DIPR.

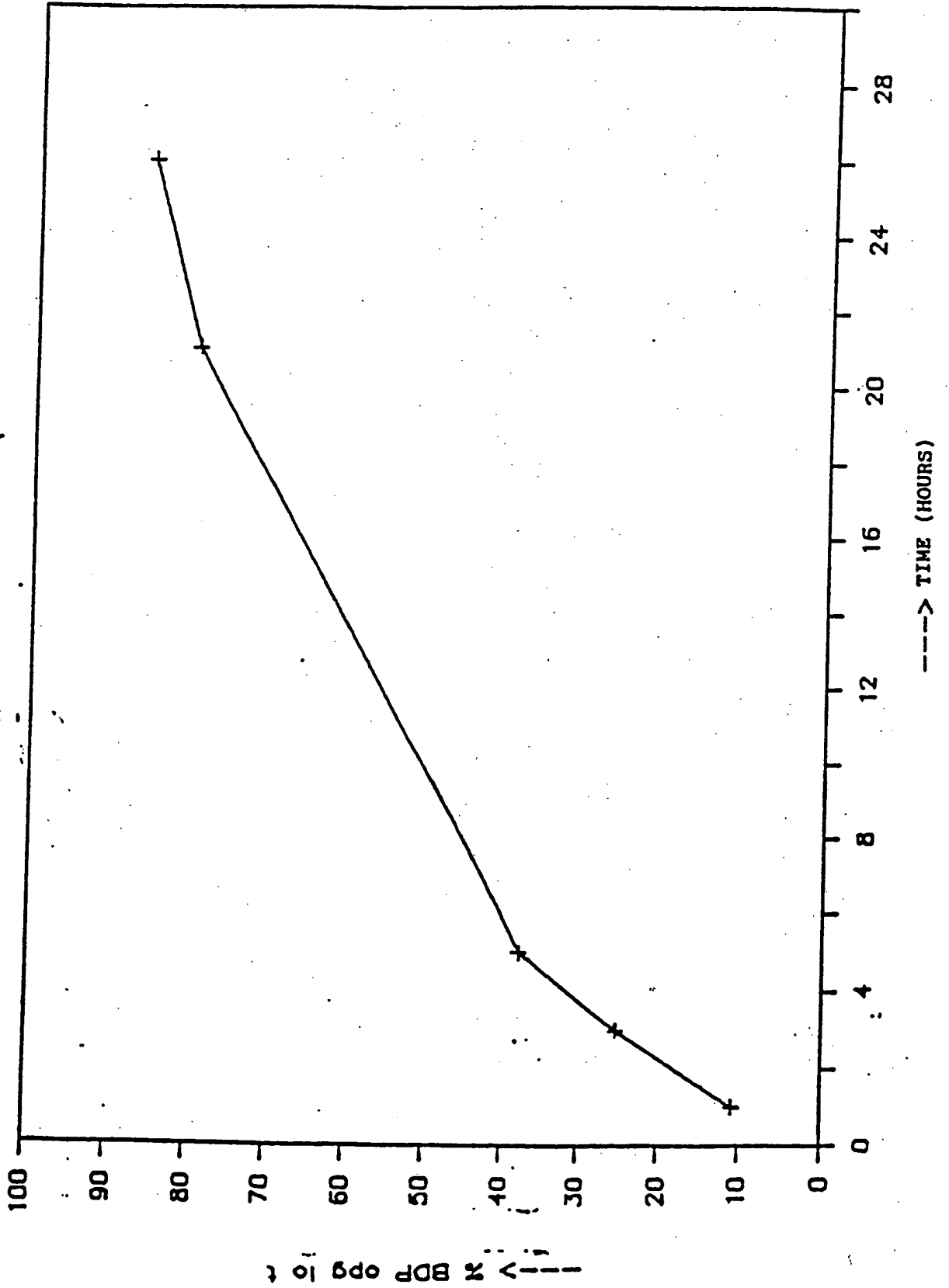
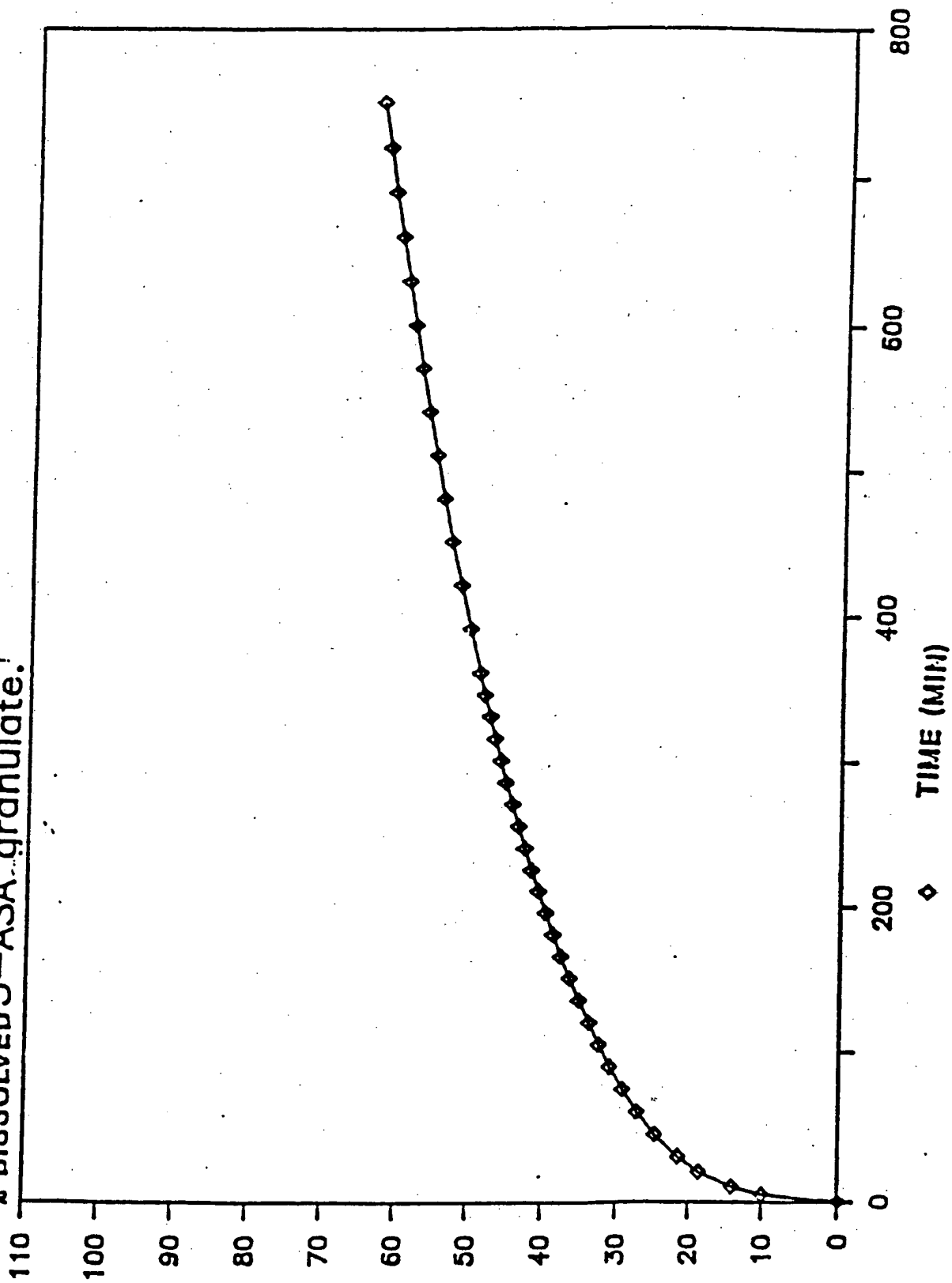




FIGURE 3

% DISSOLVED 5-ASA granulate!





DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 103, no. 1, 8 July 1985 Columbus, Ohio, USA HASEGAWA A. et al: "Application of solid dispersions of nifedipine with enteric coating agent to prepare a sustained-release dosage form" page 331; column 2; ref. no. 11390 & CHEM PHARM BULL 1985, 33(4), 1615-19 * abstract *	1-14	A61K9/18 A61K9/22
A	CHEMICAL ABSTRACTS, vol. 106, no. 14, 6 April 1987 Columbus, Ohio, USA OHNISHI N. et al: "Preparation of sustained release granules of nifedipine using a solid dispersion system and pharmacokinetic study after oral administration to rabbits." page 390; column 2; ref. no. 125780 & YAKUGAKU ZASSHI 1986, 106(12), 1131-6 * abstract *	1-14	
A	CHEMICAL ABSTRACTS, vol. 105, no. 13, 29 September 1986 Columbus, Ohio, USA OHNISHI N. et al: "Preparation of sustained release suppositories of indomethacin using a solid dispersion system and evaluation of bioavailability in rabbits." page 363; column 1; ref. no. 120643 & CHEM PHARM BULL 1986, 34(7), 2999-3004 * abstract *	1-14	TECHNICAL FIELDS SEARCHED (Int. Cl.5)  A61K
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 08 MARCH 1990	Examiner AVEDEKIAN P. F.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document</p> <p>T : theory or principle underlying the invention  F : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons</p> <p>A : member of the same patent family, corresponding document</p>			

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